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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,950	SHENOY ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/26/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-83* is/are pending in the application.

4a) Of the above claim(s) *12,14,35-38,40-42,69,72,73,77 and 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11,13,15-34,39,43-68,70,71,74-76 and 79-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.o.o

Response to the Amendment

The Amendment filed on 05/26/2005 in response to the previous Non-Final Office Action (02/24/2005) is acknowledged and has been entered.

Claims 1-3, 5-83 are currently pending.

Claims 12, 14, 40-42, 69, 72-73, and 77-78 have been withdrawn as being drawn to a non-elected invention.

Claims 35-38 have been withdrawn as being drawn to non-elected species.

Claims 1-3, 5-11, 13, 15-34, 39, 43-68, 70-71, 74-76, and 79-83 are currently under consideration.

Note: For examination purposes, the claims were interpreted as reading on the elected invention Infliximab in the following manner (see specification page 98, paragraph 0272):

Claim 8 will be interpreted as reading on a crystal of a chimeric antibody. Claim 9 will be interpreted as reading on a crystal of an IgG antibody. Claim 10 will be interpreted as reading on a crystal of an IgG1 antibody. Claim 13 will be interpreted as reading on a crystal of Infliximab. Claim 15 will be interpreted as reading on a crystal of an anti-TNF antibody. Claim 16 will be interpreted as reading on a crystal of an antibody for treating an inflammatory disease. New Claim 80 will be interpreted as reading on a crystal of a chimeric antibody. New Claim 81 will be interpreted as reading on a crystal of Infliximab. New claim 82 will be interpreted as reading on a crystal of an anti-TNF antibody. New Claim 83 will be interpreted as reading on a crystal of an antibody for treating an inflammatory disease.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Formal Matters:

Information Disclosure Statement

The Information Disclosure Statement filed on 7/11/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections Maintained:

Claims 1, 5-6, 9-11, 21-25, 31 and 33 **remain** rejected under 35 U.S.C. 102(b) as being anticipated by Harris *et al.* (Proteins: Struct. Funct. Genet. 1995; 23: 285-289) for the reasons of record in the Non Final Office Action of 2/24/2005 (pages 4-5) and for the reasons set forth below.

In reference to the previous office action which held that Harris et al discloses the crystallization of a intact monoclonal antibody, which would inherently be characterized by a β-sheet structural content and increased half-life over its soluble counterparts, Applicants (Remarks, page 24) contend that the extent of β-sheet structural content, varies widely from protein to protein and the measurement of the structural content of a crystallized protein as compared to its soluble protein counterpart is a measure of how intact the structure of the protein remains after crystallization. Thus, Applicants assert that the claims as amended, signifies that the crystals of the present invention maintain a high degree of the structure that characterizes them in their soluble state, which in turn means that these crystals retain a high degree of their functionality and can therefore be effectively used in a variety of applications, including therapeutic applications. Applicants further argue that in contrast to the antibodies of Harris, which were generated for the purpose of X-ray diffraction studies and form over long periods of time resulting in lower yields and larger dimensions, the antibody crystals of the present invention are smaller than those for X-ray diffraction studies and are grown in large scale for the purposes of therapeutic use such that the growth rate and yield of the antibody crystals are very important. Moreover, Applicants assert that the Examiner has cited no scientific basis for the conclusion that the Harris antibody crystals would inherently posses the properties of the antibody or antibody fragment crystals of the present invention. Thus, in the absence of such disclosure of scientific rationale, the antibody crystals of Harris cannot be deemed to anticipate the antibody or antibody fragment crystals of the present invention.

These arguments have been carefully considered but are not found persuasive.

First, the previous rejection was based on the technical reasoning that necessarily flowed from the teachings of the prior art- a monoclonal intact antibody crystal. Thus, while Applicants compare the size, growth rates, yields, and intended use of the antibody crystals of Harris et al as compared to the presently claimed antibodies, the claims as amended do not appear to suggest any of these limitations. Nor, do they distinguish the claimed product from the prior art. Furthermore, Applicants have not provided any evidence that the antibody crystals of Harris could not be used in a therapeutic application. The intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). As to the question of whether the antibody crystals of Harris would inherently posses the properties of the antibody or antibody fragment crystals of the present invention, i.e., the β-sheet structural counterpart and the increased half-life over its soluble counterpart, Applicants have not provided any evidence or a patentably difference between the antibody crystal of the prior art and that antibodies as claimed. The examiner acknowledges and agrees with Applicants statement that the "extent of β-sheet structural content varies widely from protein to protein (emphasis added)". However, Creighton, T.E. (Proteins: Structures and Molecular Properties, 2nd Ed., W.H. Freeman and Company, 1993) teaches that the three dimensional structure of a protein is usually not altered by its incorporation into a crystal lattice, such that there is essentially the same folded structure obtained (emphasis added) irrespective of the method of crystallization (page 202, 2nd column, 2nd paragraph). Moreover, Applicants are reminded that the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Therefore, claims 1, 4-6, 9-11, 21-25, 31 and 33 remain rejected under 35 U.S.C. 102(b) as being anticipated by Harris *et al.* (Proteins: Struct. Funct. Genet. 1995; 23: 285-289).

Claims 2, 6, 11, 20-24 and 32 **remain** rejected under 35 U.S.C. 102(b) as being anticipated by Hoedemaeker *et al.* (J. Biol. Chem. 1997; 272 (47): 29784-29789) for the reasons of record in the Non Final Office Action of 2/24/2005 (pages 5-6) and for the reasons set forth below.

In reference to the previous office action which held that Hoedemaeker *et al.* discloses a crystal of a single chain Fv fragment of a monoclonal antibody, which would inherently be characterized by a β-sheet structural content and increased half-life over its soluble counterparts, Applicants contend (Remarks, page 27) that Hoedemaeker's antibody fragment crystal, as in the case of Harris et al, was generated for the purposes of X-ray diffraction and is not characterized by the feature of β-sheet structural content, or greater half-life in vivo than its soluble counterpart which is displayed by the antibody and antibody fragment crystals of the present invention. Moreover, Applicants assert that the Examiner has cited no scientific basis for the conclusion that the Hoedemaeker antibody crystals would inherently posses the properties of the antibody or antibody fragment crystals of the present invention. Thus, in the absence of such disclosure of scientific rationale, the antibody crystals of Hoedemaeker cannot be deemed to anticipate the antibody or antibody fragment crystals of the present invention.

These arguments have been carefully considered but are not found persuasive.

First, the previous rejection was based on the technical reasoning that necessarily flowed from the teachings of the prior art- a crystal of a single chain Fv fragment of a monoclonal antibody. Thus, while Applicants compare the intended use of the antibody crystals of Hoedemaeker et al as compared to the presently claimed antibodies, the claims as amended do not appear to suggest this limitation. Thus, any argument pertaining to the intended use is not pertinent. As in the case of Harris, Applicants have not provided any evidence that the antibody crystals of Hoedemaeker could not be used in a therapeutic application. The intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). As to the question of whether the antibody crystals of Hoedemaeker would inherently posses the properties of the antibody or antibody fragment crystals of the present invention, i.e., the β-sheet structural

counterpart and the increased half-life over its soluble counterpart, Applicants have not provided any evidence or a patentably difference between the antibody crystal of the prior art and that antibodies as claimed. The examiner acknowledges and agrees with Applicants statement that the "extent of β-sheet structural content varies widely from protein to protein (emphasis added)". However, Creighton, T.E. (Proteins: Structures and Molecular Properties, 2nd Ed., W.H. Freeman and Company, 1993) teaches that the three dimensional structure of a protein is usually not altered by its incorporation into a crystal lattice, such that there is essentially the same folded structure obtained (emphasis added) irrespective of the method of crystallization (page 202, 2nd column, 2nd paragraph). Moreover, Applicants are reminded that the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Therefore, claims 1, 4-6, 9-11, 21-25, 31 and 33 remain rejected under 35 U.S.C. 102(b) as being anticipated by Harris *et al.* (Proteins: Struct. Funct. Genet. 1995; 23: 285-289).

Claims 43-68 and 74-75 **remain** and **new claim** 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Harris *et al.* (Proteins: Struct. Funct. Genet. 1995; 23: 285-289) in combination with McPherson (Eur. J. Biochem. 1990; 189: 1-23), and further in view of Pollock *et al.* (J. Immunol. Methods 1999; 231(1-2):147-57) for the reasons of record in the Non Final Office Action of 2/24/2005 (pages 10-12) and for the reasons set forth below.

In reference to the previous office action which held that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize antibody crystallization conditions in view of the teachings of McPherson, Applicants contend (Remarks, Page 31) that one or skill in the art seeking to carry out large-scale crystallization would not look to Harris or McPherson, because they relate to X-ray diffraction studies, which do not involve large scale methods of crystallization. Moreover, Applicants assert that the Examiner's obvious rejection is based on no more than a reading of Harris and McPherson in hindsight of applicants'

specification. Therefore, Applicants argue that such a hindsight perspective cannot support the asserted obviousness of the present invention.

First, the previous rejection was based on the fact that it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to optimize antibody crystallization conditions as taught by Harris et al. in view of the teachings of McPherson, wherein one would have been motivated to do so because McPherson teaches that macrocrystallization is a matter of searching, as systematically as possible, the ranges of the individual parameters that impact upon crystal formation, finding a set or multiple set of these factors that yield some kind of crystals, and then optimizing the variable sets to obtain the best possible crystals (page 1, 2nd column, 3rd paragraph). Thus, while Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, as set forth in the prior office action, Harris et al. teaches a method of crystallizing whole antibodies using the following conditions: (a) antibody concentration of 3-5 mg/mL; (b) polyethylene glycol (PEG) size of 3350 and concentration of 4-12 %; (c) buffer concentration of 10 mM; pH from 3.0 to 9.0; and (d) a temperature of 4, 18, 23, and 37°C, while McPherson discloses the current approaches to macromolecular crystallization and conveys to one of ordinary skill in the art the knowledge that is out there in the prior art referring to the crystallization of macromolecules. Although Applicants assert that one of skill in the art seeking to carry out large-scale crystallization would not look to Harris or McPherson, because they relate to X-ray diffraction studies, Applicants have not have not provided evidence or a patentable difference between the crystallization conditions disclosed by Harris et al. and the presently claimed "large-batch crystallization" conditions. Is one of skill in the art to conclude from Applicants arguments that these conditions as set forth by Harris et al. are not suitable for "large-batch crystallization" conditions? How is one of skill in the art to differentiate between conditions, which are suited for large scale and those, which are suited for X-ray diffraction? The specification discloses (page 69, line 3 to page 71, line 16) "large-batch crystallization" condition include: (a) an initial protein, e.g.

antibody, concentration of 1 to about 200 mg/mL; (b) polyethylene glycol (PEG) size of 200-40,000 and concentration of 5-40%; (c) buffer concentration of 0mM to 4M; pH from 3.0 to 10; and (d) a temperature of 4-37°C. Thus, as defined in the specification, the conditions set forth by Harris et al. for X-ray diffraction are suitable for large-batch crystallization and as such, it would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to optimize the antibody crystallization conditions as taught by Harris et al. in view of the teachings of McPherson.

New Objections:

Specification

The use of a variety of trademarks has been noted in this application, see for example, page 81, line 28 or page 96, line 5. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 4-11, 13, 15-34 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The correlation spectra determined by FTIR that is between about 0.8 and about 1.0 recited in claims 1-3 renders the claim the indefinite. The units of a correlation spectra that is between 0.8 and about 1.0 are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. In the instant case, it is unclear what units are representative of a correlation spectra.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-11, 15-34, 39, 43-68, 70-71, 74-76, 79-80 and 82-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of crystals of a whole antibody, single chain Fv fragment antibody, or Fab fragment antibody. However, the written description in this case only sets forth three antibody crystals, wherein the crystals are of the antibodies Rituximab, Infliximab and Trastuzumab.

The specification teaches (page 13, line 29 to page 14, line) that a single antibody molecule has a structure composed of two identical heavy chains covalently bound to each other and two identical light chains, each of which are covalently bound to one of the heavy chains, wherein the four chains are arranged in a classic "Y" motif such that the bottom "leg" of the "Y" is called the Fc region ("c" stands for "crystallizable or "complement binding") and the two "arms" of the "Y" are called the Fab regions. The specification further teaches (beginning on page 15, line 17 to page 19 line 7 and page 44, paragraph 0148) that specific antibodies of the invention to be crystallized include, but not limited to, any one of the five classes of antibodies found in humans, as well as chimeric, humanized, or monoclonal antibodies to name a few. With regards to the term "crystal", the specification teaches (page 23, paragraph 0068) that crystals are lattice arrays of building blocks called asymmetric units that are arranged according to well-defined symmetries into three dimensions. Thus, while the specification clearly contemplates crystals of any and/or all whole antibodies and fragments thereof, the written description (specification, beginning on page 81, Examples 1-30) only reasonably conveys three antibody crystals, wherein the crystals are of the

antibodies Rituximab, Infliximab and Trastuzumab. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of crystals of an antibody that encompass the genus nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of three crystalline antibodies is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of crystal of an antibody and/or any fragment thereof, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only three antibody crystals, wherein the crystals are of the antibodies Rituximab, Infliximab and Trastuzumab, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Margolin *et al.* (IDS, WO 99/55310, 04.11.99) of record.

Margolin *et al.* disclose the generation of stabilized protein crystals including, but limited to therapeutic proteins, such as antibodies, wherein the proteins molecular weight can range from proteins having a MW of 600 daltons to a glycoproteins at 1000 kilo Daltons (page 38, lines 13-15 and page 29, lines 14-25). The reference also discloses (page 9, line 26 to page 10, line 10) that the protein crystals constitute a particularly advantageous form for pharmaceutical dosage, wherein the crystals may be used for slow release in vivo. The WO application further provides compositions comprising the protein crystal and at least one polymeric carrier (page 16, lines 27-31). With regards to the polymeric carrier, the reference teaches that polymeric carriers include poly (amino acids) polymers (page 28, line 24 to page 29, line 10). Furthermore, Margolin *et al.* disclose protein crystal formulations comprising the protein crystal and at least one ingredient (page 16, lines 27-31) . With

regard to the ingredient, the WIPO application that an ingredient includes, but is not limited to sweetening agents such as sucrose (page 25, line 4-8). Moreover, Margolin *et al.* teach encapsulation of protein crystal formulations in polymeric carriers to make new compositions (page 42, lines 19-25). The WIPO application also provides a method of making the protein crystals and a process by which the protein crystals are dried upon filtration of the mother liquid. In addition, the reference provides protein crystals which have been cross linked in order to slow and control the release rate (page 54, lines 17-25). Lastly, Margolin *et al.* disclose that the protein crystals can be further combined with conventional materials used in controlled release administrations, including pharmaceutical controlled release administration (page 41, lines 30-34). While Margolin et al. does not specifically teach that the crystal of an antibody is characterized by a b-sheet structural content, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Creighton, T.E. (Proteins: Structures and Molecular Properties, 2nd Ed., W.H. Freeman and Company, 1993), the three dimensional structure of a protein is usually not altered by its incorporation into a crystal lattice, such that there is essentially the same folded structure obtained (page 202, 2nd column, 2nd paragraph). Secondly, although the reference does not specifically teach that the antibody crystal is a whole antibody crystal, the claims are drawn to the product *per se* and inherently, such a protein with a molecular weight between 600 dalton to 1000 kilo Dalton can be crystallized (see specification, page 12, line 30 to page 15, line 16). Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1, 3, 5, 17-18 and 70-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Navia *et al.* (US 5,849,296, 1998) of record.

In the instant case, claims 1 and 3 are drawn to a crystal of a whole antibody and a crystal of a Fab fragment of an antibody. The crystal of an antibody is further drawn to wherein the crystal

antibody is a therapeutic antibody (claim 5) or a labeled antibody (claim 17). The label is further drawn to a toxin (claim 18). Claims 70 and 71 are drawn to a diagnostic kit for the in vitro detection of an antigen in a sample, wherein the antigen may be a viral antigen.

Navia *et al.* disclose crosslinked protein crystals. Specifically, the patent teaches that protein crystals of the invention include not only entire antibodies produced against a specific antigen, but also antibody fragments such as Fab fragments (column 3, lines 54-58). Moreover, Navia *et al.* disclose (column 28, lines 52-55) that the antibody crystal can be used in a diagnostic kit. For example, Navia *et al.* teach that diagnostic antibodies allow for the detection of their corresponding targets either in vivo or in vitro (column, 32, lines 15-16). Thus, while Navia et al. does not specifically teach that the crystal of an antibody is characterized by a b-sheet structural content, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Creighton, T.E. (Proteins: Structures and Molecular Properties, 2nd Ed., W.H. Freeman and Company, 1993), the three dimensional structure of a protein is usually not altered by its incorporation into a crystal lattice, such that there is essentially the same folded structure obtained (page 202, 2nd column, 2nd paragraph). Secondly, although Navia *et al.* do not characterize the antigen as being a viral antigen, the claimed functional limitation would be an inherent property of the referenced method since the patent discusses (column 32, lines 8-14) an antibody may be one that binds to and inactivates viruses. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-11, 13, 15-16, 19-34, 39, 76 and 80-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin *et al.* (WO 99/55310, 04.11.99) of record as applied to claims 1, 5,

7, 11, 19-23, 31-34, 39 and 76 above, and further in view of Remicade (Remicade, Package Insert, August 1998) of record.

Margolin *et al.* discloses, as applied to claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 above, the generation of protein crystals and composition/formulations comprising them. Specifically, the reference discloses the generation of protein crystals, wherein the protein is an antibody.

Margolin *et al.* does not teach that the antibody is Infliximab (claim 13), which is a monoclonal (claim 6), chimeric (claim 8), IgG (claim 9), IgG1 (claim 10), anti-TNF (claim 15), antibody for treating inflammatory diseases (claim 16). Furthermore, the reference does not teach that the composition or formulation has an antibody concentration greater than about 1, 10.1, 20, 50, 100, 120, or 200 mg/mL (claims 24-30)

Remicade discloses (page 1, description) infliximab as a chimeric IgG1 monoclonal antibody which is administered as a composition/formulation at a concentration of 10 mg/mL. Specifically, the package insert teaches that infliximab binds specifically to human tumor necrosis factor alpha (TNF□) and is used primarily for the treatment of inflammatory diseases.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce an Infliximab crystal in view of the teachings of Margolin *et al.* One would have been motivated to do so because Margolin *et al.* teaches (page 8, line 27 to page 10 line 18) that crystalline forms of biological macromolecules are advantageous for storage, large scale purification, preventing interactions which occur in solution, pharmaceutical dosage (e.g., slow release formulations in vivo), and that certain variables (e.g., crystal size, shape, formulation with excipients that effect dissolution, crosslinking) can be manipulated to produce delivery vehicles for biological molecules. Thus, one of ordinary skill in the art would have a reasonable expectation of success that the production of an antibody crystal of infliximab in view teachings of Margolin *et al.*, one would achieve a stable infliximab crystal that can be easily purified and stored for extended periods of time. Furthermore, the claimed concentration of about 1, 10.1, 20, 50, 100, 120, or 200 mg/mL overlaps the referenced concentration of 10 mg/mL of Infliximab and is therefore an obvious variation of the reference teaching absent a showing of unobvious property. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
8/6/05